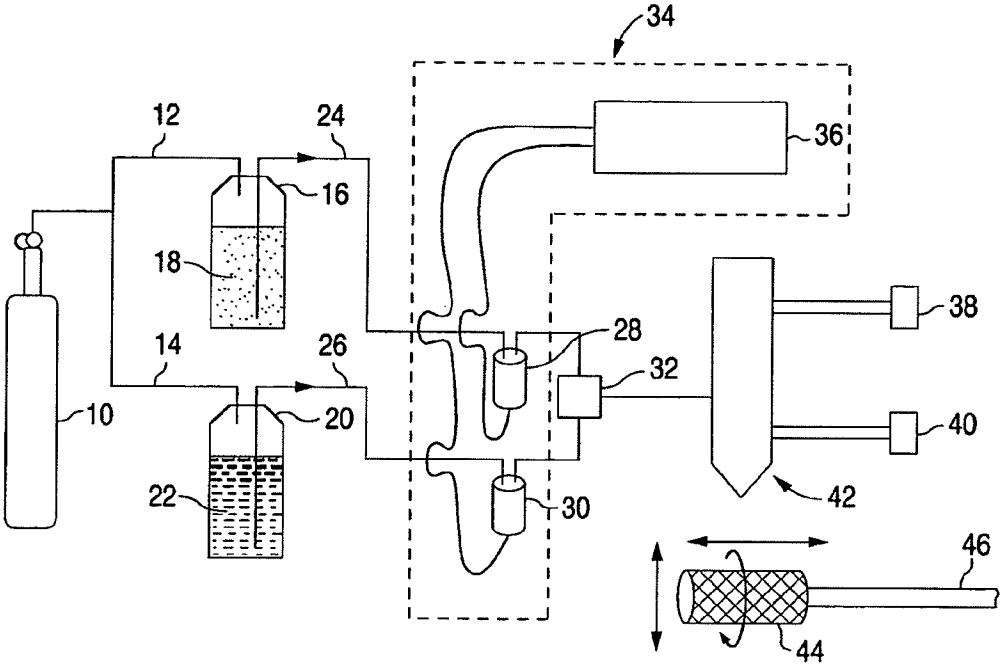
34
12
24
36
16
18
38
28
14
26
32
10
20
40
22
30
42
46
44

FIG. 1

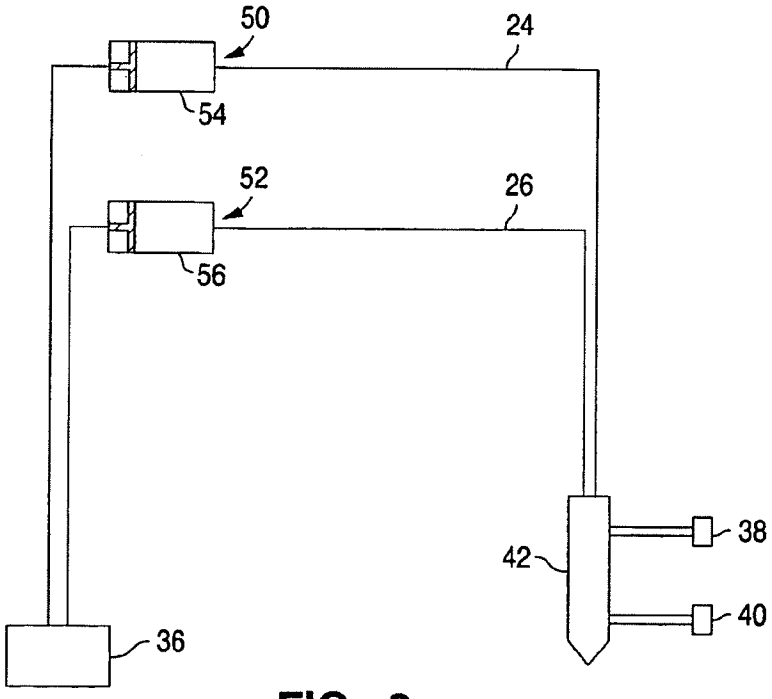
50
24
54
52
26
56
38
42
40
36

FIG. 2

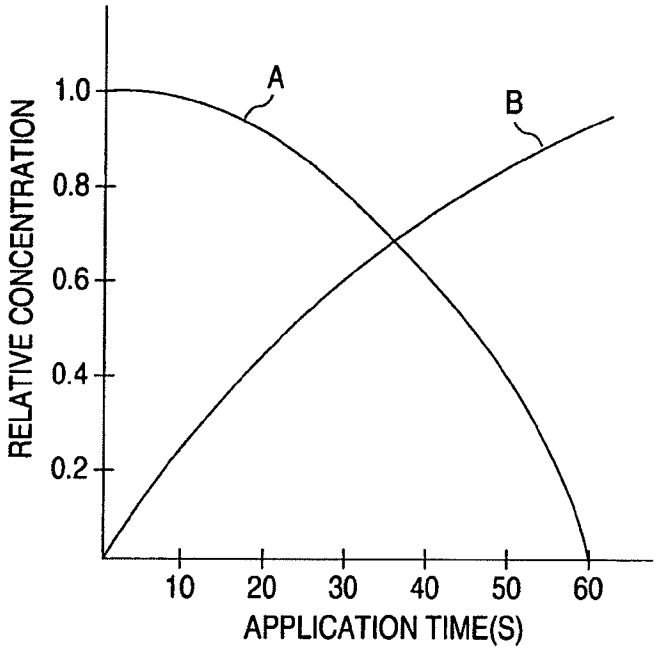
RELATIVE CONCENTRATION
1.0
0.8
0.6
0.4
0.2
A
B
10
20
30
40
50
60
APPLICATION TIME(S)

FIG. 3

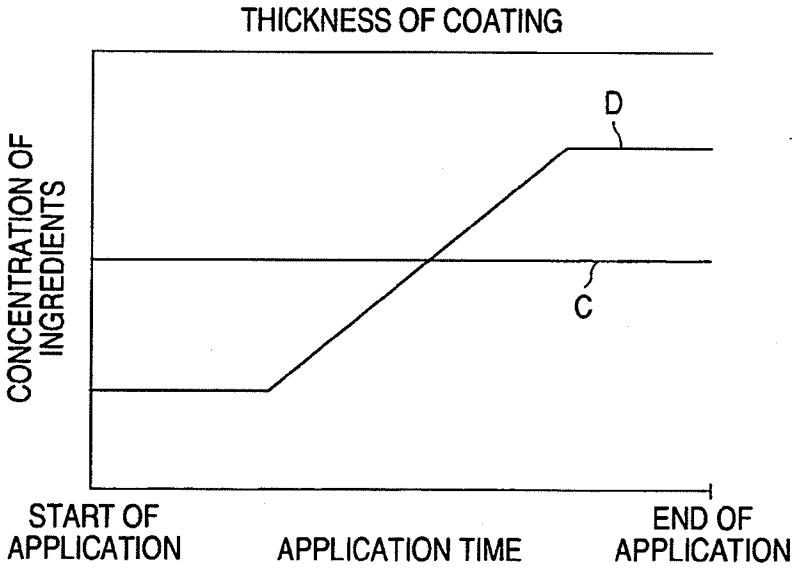
THICKNESS OF COATING
CONCENTRATION OF INGREDIENTS
D
C
START OF APPLICATION
APPLICATION TIME
END OF APPLICATION

FIG. 4

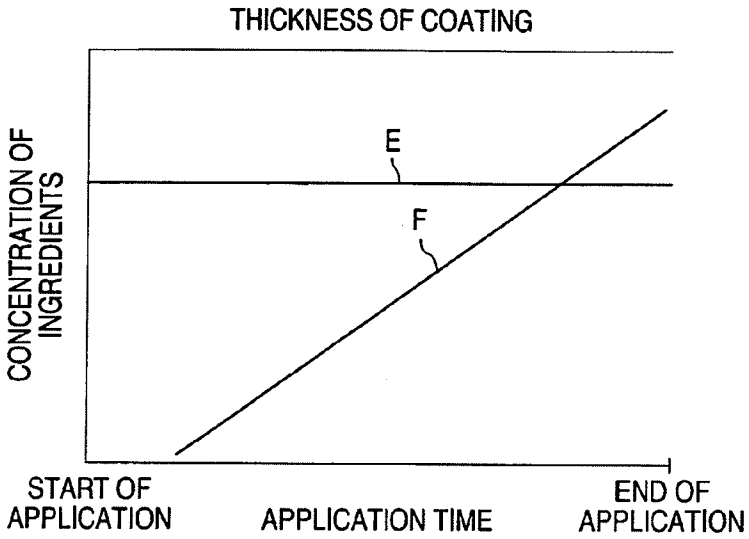
THICKNESS OF COATING
CONCENTRATION OF INGREDIENTS
E
F
START OF APPLICATION
APPLICATION TIME
END OF APPLICATION

FIG. 5

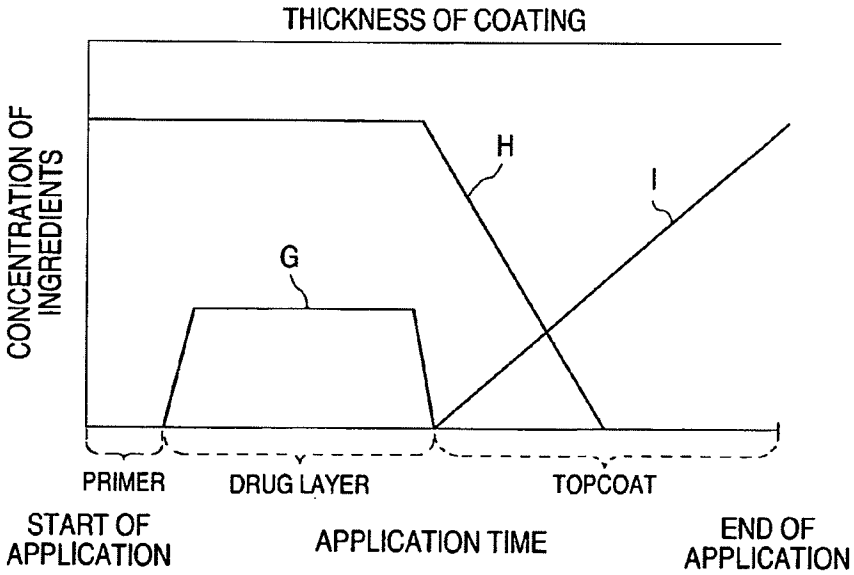
THICKNESS OF COATING
CONCENTRATION OF INGREDIENTS
H
I
G
PRIMER
DRUG LAYER
TOPCOAT
START OF APPLICATION
APPLICATION TIME
END OF APPLICATION

FIG. 6

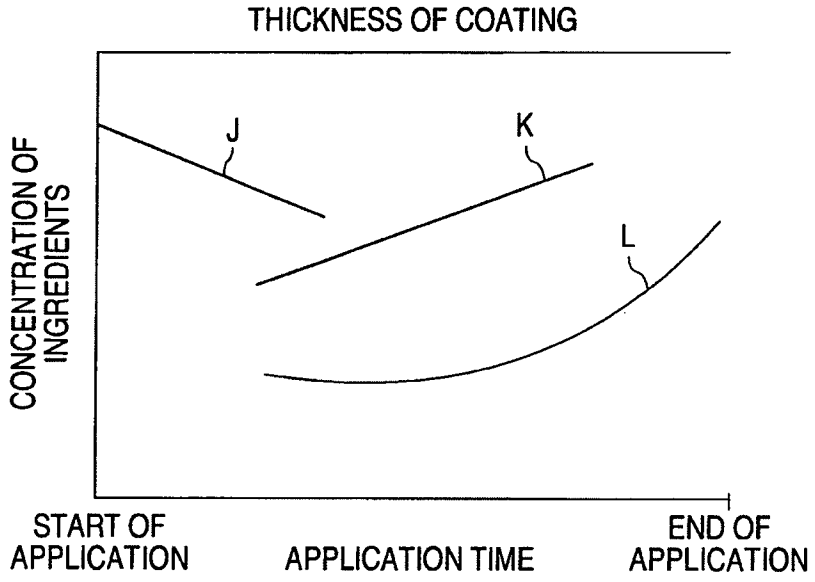
THICKNESS OF COATING
CONCENTRATION OF INGREDIENTS
J
K
L
START OF APPLICATION
APPLICATION TIME
END OF APPLICATION

FIG. 7

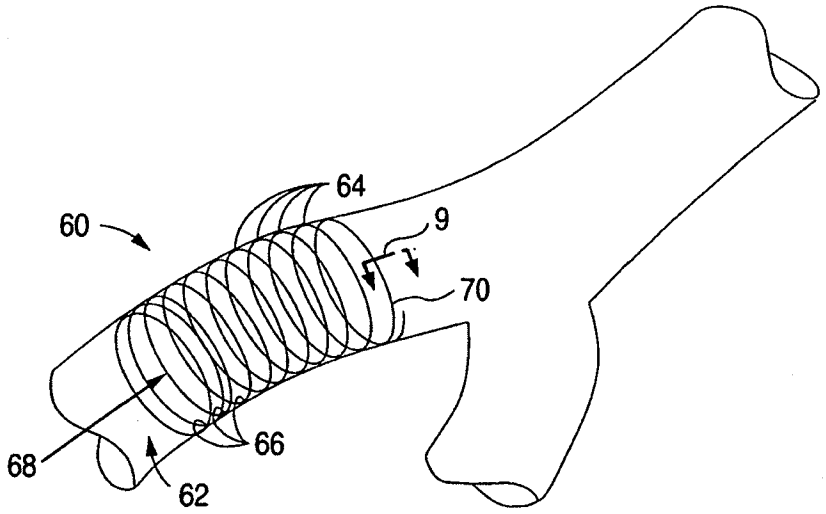
60
64
9
70
66
68
62

FIG. 8

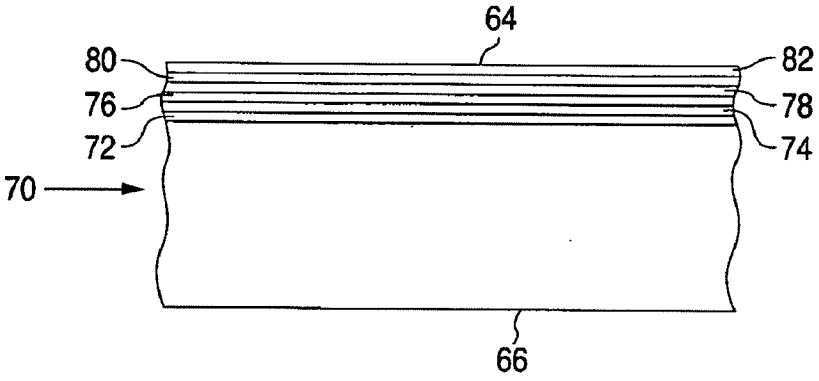

FIG. 9

APPARATUS AND METHOD FOR COATING IMPLANTABLE DEVICES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to implantable devices, such as stents. More particularly, the present invention relates to an apparatus and method for coating stents.

2. Description of the Background

Implanting a stent, after a percutaneous transluminal coronary angioplasty (PTCA) procedure, is often used to avoid or mitigate the effects of restenosis at a surgical site. In general, stents are small, cylindrical devices whose structure serves to create or maintain an unobstructed opening within a lumen. Stents are typically made of, for example, stainless steel, Nitinol or other materials and are delivered to the target site via a balloon catheter. Although the stents are effective in opening the stenotic lumen, the foreign material and structure of the stents themselves may exacerbate the occurrence of restenosis or thrombosis.

In addition to using a stent, drugs or therapeutic agents that limit migration and/or proliferation of vascular smooth muscle cells are used to significantly reduce the incidence of restenosis and thrombosis. Examples of therapeutic agents commonly used include heparin, aspirin, IIb/IIIa inhibitors, antithrombogenic agents, dexamethasone, steroids, antiinflammatory agents, cytostatic agents, cytotoxic agents, antimicrobials, thrombolytics, monoclonal antibodies, tranilast, and antifibrosis agents. Since the therapeutic agents are applied systemically to the patient, they are absorbed not only by the tissues at the target site, but by other areas of the body. As such, one drawback associated with the systemic application of drugs is that areas of the body not needing treatment are also affected. To provide more site-specific treatment, stents are frequently used as a means of delivering drugs exclusively to the target site. Drugs are suspended in tissue-compatible polymers such as silicones, polyurethanes, polyvinyl alcohol, poly(ethylene-co-vinyl alcohol), polyethylene, hydrogels, substituted methacrylates, poly (ethylene-co-vinyl acetate), and hyaluronic acid and blended mixtures thereof. By positioning the stent at the target site, the drugs can be applied directly to the area of the lumen requiring therapy.

Although stents with a drug coating have been an advance for the treatment of restenosis and other similar vascular ailments, the stents, and the methods and apparatus for their production have not yet been perfected. For instance, conventional techniques often apply a single coating of a homogenous composition that contains a mixture of a polymer and a therapeutic substance. The use of a homogenous composition may have several flaws. The polymeric portion of the coating may not be stable in the vascular environment (i.e., the polymer may leach into the blood), and may not be capable of holding a sufficient amount of the drug. In addition, conventional coatings may not have a blood compatible surface to the vascular environment. Moreover, the drug release rate of a coating made from a homogenous composition cannot be tailored to provide for different release profiles.

As an alternative to using a homogenous composition to coat a stent, some conventional techniques apply a coating to a stent that has more than one layer, with each layer having a different composition. These techniques also suffer from some flaws. For example, the different layers may not strongly adhere to each, thereby allowing one or more layer to leach into the blood or become detached creating an embolization hazard. Also, the coating process of these techniques may not be very efficient because each layer must be applied, and then dried before the next layer is applied. Finally, the application of the composition for each additional layer subsequent to the drying of the previously applied layer can cause the extraction of the drug out of the previous layer. Accordingly, the concentration of the drug will reside in the upper most layers, causing a rapid release of the drug subsequent to the implantation procedure. This "burst-effect" leads to a reduced residence time of the drug at the implantation site, which may be undesirable depending on the type of condition being treated.

Accordingly, what is needed is an apparatus and process for coating stents that does not suffer from the aforementioned drawbacks. More particularly, there is a need for a method and apparatus for coating a stent that is able to modify the coating formulation as the formulation is being applied to the stent.

SUMMARY OF THE INVENTION

The present invention is directed to a method of forming a coating on an implantable device such as a stent including applying a coating formulation to a stent, the coating formulation including a first ingredient and a second ingredient, and modifying the ratio of the first ingredient with respect to the second ingredient in the coating formulation as the coating formulation is being applied to the stent. In one embodiment, the act of applying includes spraying the coating formulation on the stent.

The present invention is further directed to a system for applying a coating on a stent, including a nozzle for spraying a composition onto a stent, a first reservoir in fluid communication with the nozzle for supplying a first ingredient of the composition to the nozzle, a second reservoir in fluid communication with the nozzle for supplying a second ingredient of the composition to the nozzle, and a control assembly for adjusting the amount of the first or second ingredient that is fed into the nozzle wherein the amount of the first or second ingredient that is sprayed by the nozzle can be modified by the control assembly without interrupting the application of the composition onto the stent. The system may further have a mixer for mixing the first ingredient with the second ingredient. In one embodiment, the control assembly includes a valve for adjusting the input rate of the first or second ingredient to the nozzle.

The present invention is also directed to an implantable medical device having a coating having a first ingredient and a second ingredient, wherein from a deep region of the coating to a more shallow region of the coating, the ratio of the concentration of the first ingredient to the concentration of the second ingredient gradually increases or decreases.

In the embodiments of the present invention, the ingredients can be a polymeric material and a therapeutic substance. Some examples of polymeric materials can include ethylene vinyl alcohol copolymer, polybutylmethacrylate, polyethylene glycol, amorphous Teflon, and poly(ethylene-co-vinyl acetate). Some examples of therapeutic substances can include actinomycin D, paclitaxel, docetaxel, rapamycin, β-estradiol and BAK Heparin.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** illustrates a coating system for forming a coating on a stent;

FIG. **2** illustrates a coating system for forming a coating on a stent;

FIG. **3** is a graph showing the relative concentration of two ingredients as a function of application time;

FIGS. **4** and **5** are graphs, in accordance with two embodiments, showing the concentration of two ingredients as a function of application time and thickness of the coating;

FIGS. **6** and **7** are graphs, in accordance with other embodiments, showing the concentration of three ingredients as a function of application time and thickness of the coating;

FIG. **8** is a diagram of an embodiment of an implantable medical device inserted into a body vessel; and

FIG. **9** illustrates a partial cross-section of a strut, in accordance with one exemplary embodiment, along the line **9**—**9** of FIG. **8**.

DETAILED DESCRIPTION OF THE EMBODIMENTS

System for Coating

An embodiment of the present invention involving a system for spray coating an implatable device such as a stent is depicted in FIG. **1**. Although a spray system is depicted in the spirit of convenience and brevity, it should be noted that other systems and methods are also within the scope of the claimed invention.

Referring to FIG. **1**, a gas source such as an air compressor **10** may provide air pressure to a first reservoir **16** and a second reservoir **20** through a first air hose **12** and a second air hose **14**, respectively. First reservoir **16** can hold a first solution **18** which includes a first ingredient (e.g., a polymeric material) and a solvent. Second reservoir **20** can hold a second solution **22** which includes a second ingredient (e.g., a therapeutic substance) and a solvent. It is understood that any number of reservoirs can be used to contain any number of ingredients. The air pressure delivered from air compressor **10** can be sufficiently high enough to promote uptake of the solutions in first reservoir **16** and second reservoir **20** into a first fluid hose **24** and a second fluid hose **26**. First solution **18** and second solution **22**, in turn, can be fed into a control assembly **34**, which controls the rate that compositions from first reservoir **16** and second reservoir **20** are delivered to a mixer **32**.

First solution **18** and second solution **22** are mixed in mixer **32**, and then moved as a mixed solution to a nozzle **42**. As the mixed solution enters the chamber of nozzle **42**, the mixed solution is exposed to pressurized air from two sources: an actuating gas source **38** and an atomizing gas source **40**. Atomizing gas source **40**, which can deliver air or another gas, provides sufficient pressure and velocity to atomize the solution into small droplets. Actuating gas source **38**, on the other hand, can provide a sufficient amount of pressure so that the droplets are forced out of nozzle **42** and directed to a target (e.g., a stent).

As noted above, control assembly **34** can monitor and control the rate of fluid delivered to mixer **32** and nozzle **42**. Control assembly **34** can have a controller **36** (e.g., a CPU) that is in communication with a first valve **28** and a second valve **30**. First valve **28** and second valve **30** may be, for example, high precision proportioning valves as is well known and commonly available to those of ordinary skill in the art. Alternatively, first valve **28** and second valve **30** could be very low volume, high speed valves (Lee Electro-Fluidic Systems, Westbrook, Conn.).

In another embodiment, referring to FIG. **2**, a first reservoir **54** and a second reservoir **56** are in fluid communication with nozzle **42** for delivering two different ingredients to

nozzle **42**. Instead of a gas source such as air compressor **10**, a first syringe pump **50** and a second syringe pump **52** may provide pressure to first reservoir **54** and second reservoir **56**, respectively. Syringe pumps **50** and **52**, in turn, are in communication with controller **36**. Controller **36** may provide signals to syringe pumps **50** and **52** and control the amount of motive force that syringe pumps **50** and **52** provide to reservoirs **54** and **56**, thereby controlling the amount of ingredients that are ultimately delivered to nozzle **42**.

Various approaches may be used to mix the ingredients delivered by the reservoirs. In one embodiment, referring to FIG. **1**, the ingredients are mixed in mixer **32** before they are delivered to nozzle **42**. Representative examples of types of mixers that can be employed include an ultrasonic mixer having a piezoelectric transducer, a static mixer and a mechanical mixer. Alternatively, the ingredients can be mixed as the ingredients are introduced into and/or ejected out from nozzle **42**.

Various structures can be used to support the stents while they are being sprayed by nozzle **42**. By way of example, and not limitation, a stent **44** (FIG. **1**) can be attached to a mandrel **46** that rotates and/or moves in a linear direction during the application process. Alternatively, nozzle **42** can pivotly rotate around and move linearly along a stationary stent.

Method of Applying Coating

In one embodiment of the present invention, a method is used to apply a coating formulation to a stent, whereby the coating formulation has at least two ingredients and the relative concentrations of the ingredients are modified as the coating formulation is applied to the stent. In one embodiment, the coating formulation is applied to the stent by spraying. Referring to FIG. **1**, first solution **18** can contain a first ingredient (e.g., a polymeric material), and second solution **22** can contain a second ingredient (e.g., a therapeutic substance). A gas source such as air compressor **10** can provide the motive force to deliver first solution **18** and second solution **22** to first valve **28** and second valve **30**, respectively. Control assembly **34** can be used to control the amount of first solution **18** and second solution **22** that is delivered to mixer **32**, and ultimately the amount delivered to nozzle **42**. For example, while nozzle **42** is spraying a stent, controller **36** can modify the ratio of first solution **18** with respect to second solution **22** by controlling the operation of first and second valve **28** and **30**.

In one embodiment, for example, first solution **18** contains ingredient A (a therapeutic substance), and second solution **22** contains ingredient B (a polymeric material). While nozzle **42** is spraying stent **44**, controller **36** can send signals to first valve **28** to reduce the flow rate of first solution **18**. As a result, the amount of first solution **18**, and therefore ingredient A, that is delivered to mixer **32** is reduced, thereby modifying the contents of the composition of the coating formation that is sprayed onto stent **44**. In addition, while nozzle **42** is spraying stent **44**, controller **36** can send signals to second valve **30** to increase the flow rate of second solution **22**. For example, as shown in FIG. **3**, at the early segments of the application process, the concentration of ingredient A relative to the concentration of ingredient B is significantly higher. However, as the application process proceeds, the concentration of ingredient B can be incrementally increased while the concentration of ingredient A is concurrently decreased relative to the concentration of ingredient B.

In another embodiment, the coating formulation contains ingredient C and ingredient D. Referring to FIG. **4**, the concentration of ingredient C can remain constant as the coating is applied, while the concentration of ingredient D remains constant for an initial period, then increases, and then becomes constant at a later stage of the application.

In yet another embodiment, the coating formulation can contain ingredient E and ingredient F. Referring to FIG. **5**, ingredient E can first be applied as a primer, and then ingredient F can be gradually mixed with ingredient E at an increasing concentration.

In one exemplary implementation of the ingredients of FIG. **5**, ingredient E can be ethylene vinyl alcohol copolymer (EVAL), and ingredient F can be polyethylene glycol (PEG). EVAL is considered to have relatively good adhesion potential, whereas PEG is considered to have relatively high blood compatibility. A single coating with a large fraction of PEG relative to EVAL would likely give high blood compatibility but would swell significantly, perhaps dissolving off of the stent, releasing PEG into the blood, and generally not adhering well to the stent. A formulation with a high percentage of EVAL, in turn, would likely adhere to the stent surface, but would not be as blood compatible as PEG. In order to realize the benefits of combining EVAL and PEG, one could apply a coating formulation as shown in FIG. **5**.

In another embodiment, the coating formulation contains ingredient G, ingredient H and ingredient I. By way of example and not limitation, ingredient G can be a therapeutic substance, ingredient H can be EVAL, and ingredient I can be poly(ethylene-co-vinyl acetate). Referring to FIG. **6**, ingredient H can be first applied to the stent at constant concentration as a primer. Then, ingredient G can be added with an increasing concentration to provide a drug layer. About one-half the way through the application process, ingredient I is added to the coating formulation. The concentration of ingredient I increases through the rest of the coating process, while the concentration of ingredient H decreases. At the end of the coating process, with respect to ingredient G, ingredient H and ingredient I, the coating formulation only contains ingredient I, thereby providing a topcoat layer.

In another embodiment, the coating formulation contains ingredient J, ingredient K and ingredient L. Referring to FIG. **7**, ingredient J is initially applied to a stent as a primer. However, as the application process continues, the concentration of ingredient J in the coating formulation decreases. While ingredient J is being applied, ingredients K and L are added to the coating formulation, and the concentrations of ingredient K and L increase throughout the remainder of the coating application. For example, ingredient J is polybutylmethylmethacrylate (PBMA), ingredient K is EVAL and ingredient L is Actinomycin D, with the common solvent dimethylacetamide.

Implantable Device

A stent is broadly intended to include self-expandable stents, balloon-expandable stents, and stent-grafts. One of ordinary skill in the art, however, understands that other medical devices on which a polymeric material can be coated can be used with the practice of the present invention, such as grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, axius coronary shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, Pa. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

FIG. **8** illustrates an implantable prosthetic medical device. In the spirit of convenience and brevity, the medical device referenced in the text and figures of the present disclosure is a stent **60**. Stent **60** can be cylindrical or tubular in shape, and can be inserted into a body lumen **62**. The structure of stent **60** should allow stent **60** to be inserted into and physically uphold an anatomical passageway such as body lumen **62**, by exerting a radially outward-extending force against the walls or inner lumen surface of the passageway. If desired, stent **60** can also expand the opening of lumen **62** to a diameter greater than its original diameter and, thereby, increase fluid flow through lumen **62**.

Stent **60** can include struts **70** that form a network structure. Struts **70** have an outer (or lumen contacting) surface **64** and an inner surface **66**, as shown in FIG. **8**. In addition, a hollow bore **68** extends longitudinally through the body structure of stent **60**.

In one embodiment of the present invention, a coating formulation with a first ingredient and a second ingredient is used to coat outer surface **64** of struts **70**, and the resultant coating has a first region and a second region, where the quantity of the first ingredient with respect to the second ingredient is different in the first region as compared to the second region. In another embodiment, the coating formulation has three or more different ingredients. In a further embodiment, the coating has three or more different regions. Referring to FIG. **9**, by way of illustration, the coating of strut **70** has a first region **72**, a second region **74**, a third region **76**, a fourth region **78**, a fifth region **80** and a sixth region **82**. In the interests of brevity and simplification, the different regions are illustrated only on outer surface **64** of strut **70**. However, one of ordinary skill in the art will understand that the coating can also be on inner surface **66** of strut **70**, as well as all other surfaces of stent **60**.

Referring to FIG. **9**, first region **72** may be used as a primer, and fifth region **80** may used as a rate reduction membrane to reduce the release rate of a therapeutic substance contained in second region **74**, third region **76**, and fourth region **78**. Sixth region **82** may be used as a blood compatible layer. Furthermore, by gradually changing the concentration of the ingredients contained in the regions, there may be increased interlayer adhesion. For instance, second region **74**, third region **76**, fourth region **78**, and fifth region **80** can be used for increased interlayer adhesion between first region **72** and sixth region **82**. One of ordinary skill in the art will understand that fewer than six regions or more than six regions may be applied as part of the present invention.

By way of example, the coating formulation may include ingredient M, ingredient N, ingredient O and ingredient P. Referring to Table I, for instance, the concentrations of the various ingredients relative to each other may be changed in the different regions.

TABLE I

Region	Concentration Relative to Other Ingredients (%) Ingredient M	Ingredient N	Ingredient O	Ingredient P
First Region 72	100	0	0	0
Second Region 74	60	20	20	0
Third Region 76	30	30	30	10
Fourth Region 78	10	40	30	20
Fifth Region 80	0	50	25	25
Sixth Region 82	0	40	20	40

In yet another embodiment of the present invention, the coating formulation includes ingredient Q, ingredient R, ingredient S and ingredient T. Referring to Table II, for example, the concentrations of the various ingredients may be changed in the different regions. In one exemplary implementation of the ingredients of Table II, ingredient Q is PBMA, ingredient R is EVAL, ingredient S is Actinomycin D, and ingredient T is PEG (molecular weight 15,000 amu).

TABLE II

Region	Concentration (mg/ml) Ingredient Q	Ingredient R	Ingredient S	Ingredient T
First Region 72	1100	0	0	0
Second Region 74	733	380	0	0
Third Region 76	367	760	0	0
Fourth Region 78	0	1026	114	0
Fifth Region 80	0	1140	0	0
Sixth Region 82	0	977	0	163

The pure PBMA in first region **72** can act as a primer and afford good adhesion with the stent surface. Also, one disadvantage of the current coating processes is that there is poor interlayer compatibility among some components, such as polymeric materials. Certain polymeric materials, for instance, do not properly adhere to each other when they are applied in layers in their pure form. The graduated interface between the PBMA and EVAL in regions **72**, **74** and **76**, as depicted numerically in Table II, may provide better interlayer adhesion.

In a further embodiment of the present invention, the coating formulation includes ingredient U, ingredient V, ingredient W and ingredient X. In one exemplary implementation of the ingredients of Table III, ingredient U is PBMA, ingredient V is EVAL, ingredient W is β-Estradiol, and ingredient X is the benzylalkonium salt of heparin (BAK Heparin).

TABLE III

Region	Concentration (mg/ml) Ingredient U	Ingredient V	Ingredient W	Ingredient X
First Region 72	0	1140	0	0
Second Region 74	0	760	380	0
Third Region 76	550	570	0	0
Fourth Region 78	1100	0	0	0
Fifth Region 80	550	570	0	0
Sixth Region 82	0	1026	0	114

Composition of Coating Formulation

The ingredients contained in the coating formulation can be prepared by conventional methods. More particularly, in accordance to one embodiment, a predetermined amount of a polymeric material or combination of polymeric materials can be added to a predetermined amount of a solvent or a combination of solvents. If necessary, heating, stirring and/or mixing can be employed to effect dissolution of the polymeric material(s) into the solvent(s)—for example in an 80° C. water bath for two hours.

A therapeutic substance can be also be an ingredient contained in the coating formulation. In accordance to one embodiment, a predetermined amount of a therapeutic substance or combination of therapeutic substances can be added to a predetermined amount of a solvent, a combination of solvents, with or without a polymeric material. The therapeutic substance should be in true solution or saturated in the composition of the coating formulation. If the therapeutic substance is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. The therapeutic substance may be added so that dispersion is in fine particles. The mixing of the therapeutic substance can be conducted at ambient pressure and at room temperature.

Representative examples of polymeric material that can be used to coat a medical device in accordance with the present invention include ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL); polybutylmethacrylate; poly(hydroxyvalerate); poly(L-lactic acid); polycaprolactone; poly(lactide-co-glycolide); poly(hydroxybutyrate); poly(hydroxybutyrate-co-valerate); polydioxanone; polyorthoester; polyanhydride; poly(glycolic acid); poly(D,L-lactic acid); poly(glycolic acid-co-trimethylene carbonate); polyphosphoester; polyphosphoester urethane; poly(amino acids); cyanoacrylates; poly(trimethylene carbonate); poly(iminocarbonate); copoly(ether-esters) (e.g., PEO/PLA); polyalkylene oxalates; polyphosphazenes; biomolecules, such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid; polyurethanes; silicones; polyesters; polyolefins; polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxym-

ethylenes; polyimides; polyethers; epoxy resins; polyurethanes; rayon; rayon-triacetate; cellulose; cellulose acetate; cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; amorphous Teflon; and carboxymethyl cellulose. EVAL is functionally a very suitable choice of polymeric material. The copolymer possesses good adhesive qualities to the surface of a stent, particularly stainless steel surfaces, and has illustrated the ability to expand with a stent without any significant detachment of the copolymer from the surface of the stent. The copolymer, moreover, allows for good control capabilities over the release rate of the therapeutic substance.

Representative examples of solvents include chloroform, acetone, water (buffered saline), dimethylsulfoxide (DMSO), propylene glycol methyl ether (PM), iso-propylalcohol (IPA), n-propylalcohol, methanol, ethanol, tetrahydrofuran (THF), dimethylformamide (DMF), dimethyl acetamide (DMAC), benzene, toluene, xylene, hexane, cyclohexane, heptane, octane, nonane, decane, decalin, ethyl acetate, butyl acetate, isobutyl acetate, isopropyl acetate, butanol, diacetone alcohol, benzyl alcohol, 2-butanone, cyclohexanone, dioxane, methylene chloride, carbon tetrachloride, tetrachlroro ethylene, tetrachloro ethane, chlorobenzene, 1,1,1-trichloroethane, formamide, pentane, trifluoroethanol, hexafluoroisopropanol, freon, hexamethylphosphorus triamide, and combinations thereof.

The therapeutic substance can be for inhibiting the activity of vascular smooth muscle cells. More specifically, the therapeutic substance can be aimed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells for the inhibition of restenosis. The therapeutic substance can also include any substance capable of exerting a therapeutic or prophylactic effect in the practice of the present invention. For example, the therapeutic substance can be for enhancing wound healing in a vascular site or improving the structural and elastic properties of the vascular site. Examples of therapeutic substances include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, Wis. 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (Taxotere®, from Aventis S. A., Frankfurt, Germany), methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g., Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax ä (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, N.J.), calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, N.J.), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, rapamycin and dexamethasone. The foregoing substances are listed by way of example and are not meant to be limiting. Other therapeutic substances which are currently available or that may be developed in the future are equally applicable.

The dosage or concentration of the therapeutic substance required to produce a favorable therapeutic effect should be less than the level at which the therapeutic substance produces toxic effects and greater than the level at which non-therapeutic results are obtained. The dosage or concentration of the therapeutic substance required to inhibit the desired cellular activity of the vascular region can depend upon factors such as the particular circumstances of the patient; the nature of the trauma; the nature of the therapy desired; the time over which the ingredient administered resides at the vascular site; and if other therapeutic agents are employed, the nature and type of the substance or combination of substances. Therapeutic effective dosages can be determined empirically, for example by infusing vessels from suitable animal model systems and using immunohistochemical, fluorescent or electron microscopy methods to detect the agent and its effects, or by conducting suitable in vitro studies. Standard pharmacological test procedures to determine dosages are understood by one of ordinary skill in the art.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from the embodiments this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of the embodiments this invention.

What is claimed is:

1. A method of forming a coating on an implantable medical device, comprising:

applying a coating formulation to an implantable medical device, the coating formulation including a first ingredient, a second ingredient and a third ingredient; and

modifying the ratio of at least two of the ingredients with respect to each other in the coating formulation while the coating formulation is being supplied to a coating dispenser for discharging onto the device.

2. The method of claim **1**, wherein the coating formulation is applied to form a coating that includes a first region, a second region and a third region.

3. The method of claim **2**, wherein the first ingredient is a first polymeric material, the second ingredient is a second polymeric material, and the third ingredient is a therapeutic substance, and wherein the first region is free from the second polymeric material, and the third region is free from the first polymeric material and the therapeutic substance.

4. The method of claim 1, wherein the modifying comprises maintaining the amount of at least one of the first, second or third ingredients constant.

5. The method of claim 1, wherein the amount of at least one of the first, second or third ingredients in the coating formulation increases or decreases at a constant rate as the coating formulation is being applied to the device.

6. The method of claim 1, wherein the applying comprises spraying the coating formulation on the device.

7. A method of forming a coating on an implantable medical device, comprising:

applying a coating formulation to an implantable medical device, the coating formulation including a first ingredient and a second ingredient; and

modifying the ratio of the first ingredient with respect to the second ingredient to form regions of a coating having a graduated interface between the first and second ingredients, wherein the modification occurs without interrupting the application of the coating formulation onto the device from a coating dispenser.

8. The method of claim 7, wherein the first ingredient comprises a polymer and the second ingredient comprises a drug.

9. The method of claim 7, wherein the first ingredient comprises a first polymer and the second ingredient comprises a second polymer.

10. The method of claim 7, wherein the modification is conducted by a controller and at least on valve.

11. The method of claim 7, wherein the first and second ingredients are mixed and modified in a mixer prior to being supplied to the coating dispenser.

12. The method of claim 7, wherein the first ingredient comprises a polymer dissolvent in a solvent and the second ingredient comprises a drug in a fluid carrier.

13. The method of claim 7, wherein the coating dispenser comprises a spray applicator.

14. The method of claim 7, additionally comprising, supplying the first ingredient from a first supply source to the coating dispenser and supplying the second ingredient from a second supply source to the coating dispenser such that a valve controls the amount of the first ingredient being supplied to the coating dispenser.

15. The method of claim 14, wherein the first and second ingredients are supplied into a mixer prior to being supplied to the coating dispenser.

16. The method of claim 14, wherein a second valve controls the amount of the second ingredient being supplied to the coating dispenser.

17. The method of claim 16, wherein the first and second ingredients are supplied into a mixer prior to being supplied to the coating dispenser.

18. The method of claim 7, wherein the device is a stent.

19. A method of forming a coating on a stent, comprising:

applying a coating formulation from a coating dispenser to a stent, the coating formulation including a first ingredient and a second ingredient; and

modifying the ratio of the first ingredient with respect to the second ingredient in the coating formulation while the coating formulation is being discharged out from the coating dispenser and onto the stent.

20. The method of claim 19, wherein the act of applying comprises spraying the coating formulation on the stent.

21. A stent comprising a coating produced in accordance with the method of claim 19, wherein the coating has a first region and a second region wherein the quantity of the first ingredient with respect to the second ingredient is different in the first region as compared to the second region.

22. The method of claim 19, wherein the first ingredient comprises a polymer and the second ingredient comprises a therapeutic substance.

23. The method of claim 22, wherein the polymer is selected from the group consisting of an ethylene vinyl alcohol copolymer, poly(butylmethacrylate), poly(ethylene glycol), amorphous Teflon, and poly(ethylene-co-vinyl acetate).

24. The method of claim 22, wherein the therapeutic substance is selected from the group consisting of actinomycin D, paclitaxel, docetaxel, rapamycin, β-estradiol and BAK Heparin.

25. The method of claim 19, wherein the first ingredient comprises a first polymer and the second ingredient comprises a second polymer.

26. The method of claim 19, wherein the ratio is modified by gradually increasing the concentration of the first ingredient in the coating formulation from the initiation of the application of the coating formulation to the stent until the termination of the application of the coating formulation to the stent.

27. The method of claim 19, wherein the first and second ingredients are different therapeutic substances.

28. The method of claim 19, wherein the modifying comprises maintaining the amount of the first ingredient constant and increasing or decreasing the amount of the second ingredient.

29. The method of claim 19, wherein the coating formulation is applied to form a coating that includes a first region and a second region above the first region, and wherein the first region is free from the second ingredient.

30. The method of claim 29, wherein the first ingredient is a first polymeric material and the second ingredient is a second polymeric material, and wherein the first polymeric material is for increasing the adhesion of the coating on the stent, and the second polymeric material is for increasing the blood compatibility of the coating.

31. The method of claim 19, wherein the coating formulation additionally includes a third ingredient.

32. The method of claim 31, additionally comprising modifying the amount of the third ingredient as the coating formulation is being applied to the stent.

33. The method of claim 31, additionally comprising modifying the ratios of the first, second and third ingredients with respect to each other as the coating formulation is being applied to the stent.

34. The method of claim 31, wherein during the modifying, the amount of the third ingredient is keep constant.

35. The method of claim 31, wherein the first ingredient is a polymer, the second ingredient is a drug and the third ingredient is a solvent.

36. The method of claim 31, wherein the first ingredient is a first polymer, the second ingredient is a second polymer, and the third ingredient is a solvent.

37. The method of claim 31, wherein applying is by spraying.

38. The method of claim 31, wherein the first, second and third ingredients can each be any one of a polymer, a drug or a solvent.

39. The method of claim 19, wherein the amount of the first ingredient is zero at the start of the application of the coating formulation.

40. The method of claim 39, wherein the first ingredient is a drug.

41. The method of claim 19, wherein the amount of the first ingredient is zero at the start of the application of the coating formulation and sometime thereafter.

42. The method of claim 41, wherein the first ingredient is a drug.

43. The method of claim 19, wherein the modification is controlled by a computer.

44. The method of claim 19, wherein the modification comprising adjusting the amount of the first and/or second ingredient that is supplied to the coating dispenser.

45. The method of claim 44, wherein the amount of the first and/or second ingredient that is supplied to the coating dispenser is controlled by at least one valve so as to modify the ratio between the first and second ingredients.

46. The method of claim 45, wherein the at least one valve is in communication with a controller for controlling the operation of the at least one valve.

47. The method of claim 19, wherein

the first ingredient is contained in a first source in fluid communication with a mixer, and

the second ingredient is contained in a second source in fluid communication with the mixer, the mixer being in communication with the coating dispenser, wherein the ratio of the first ingredient with respect to the second ingredient is adjusted at the mixer prior to being supplied into the coating dispenser.

48. The method of claim 47, wherein the amount of the first ingredient supplied to the mixer is controlled by a first valve and the amount of the second ingredient supplied to the mixer is controlled by a second valve.

49. The method of claim 19, wherein the first ingredient comprises at least one polymer and at least one solvent and the second ingredient comprises at least one polymer and at least one solvent.

50. The method of claim 19, wherein the coating dispenser comprises an atomized spray nozzle.

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US007217286B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,217,286 B2**
(45) **Date of Patent: *May 15, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/467,035**

(22) Filed: **Aug. 24, 2006**

(65) **Prior Publication Data**

US 2007/0021825 A1 Jan. 25, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/951,385, filed on Sep. 28, 2004, which is a continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.45–1.48; 427/2.1–2.31
See application file for complete search history.

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(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets

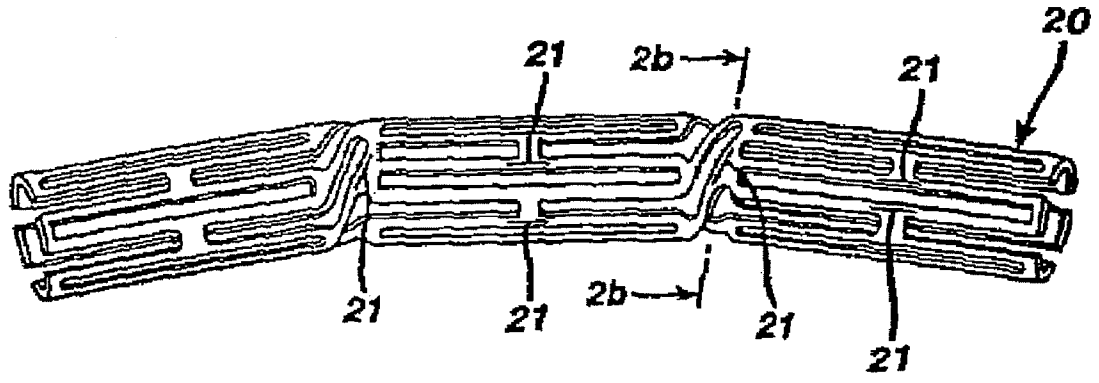

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FIG. 1

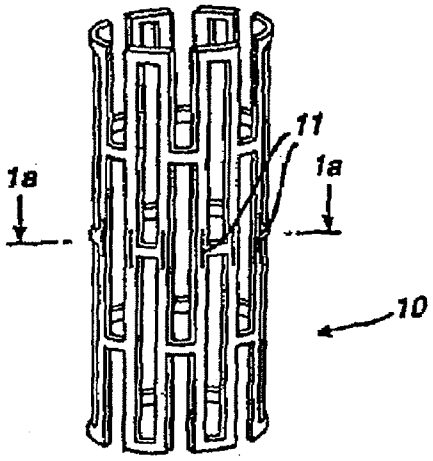


FIG. 1a

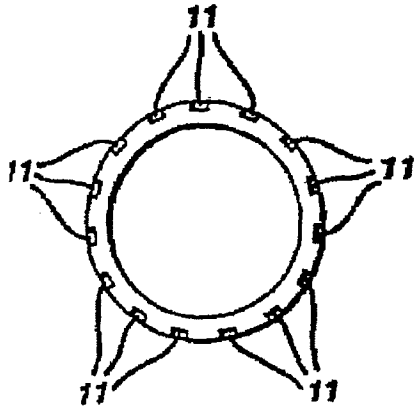


FIG. 2a

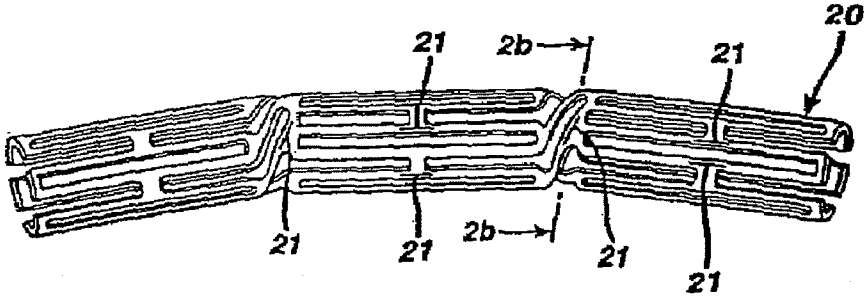


FIG. 2b

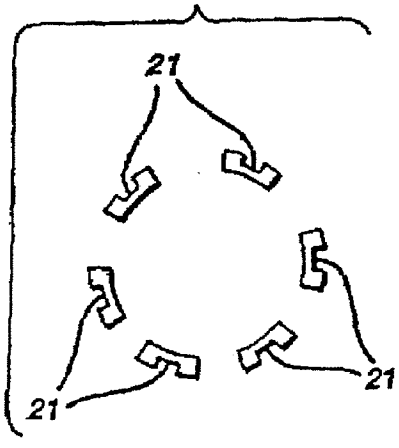


FIG. 3a

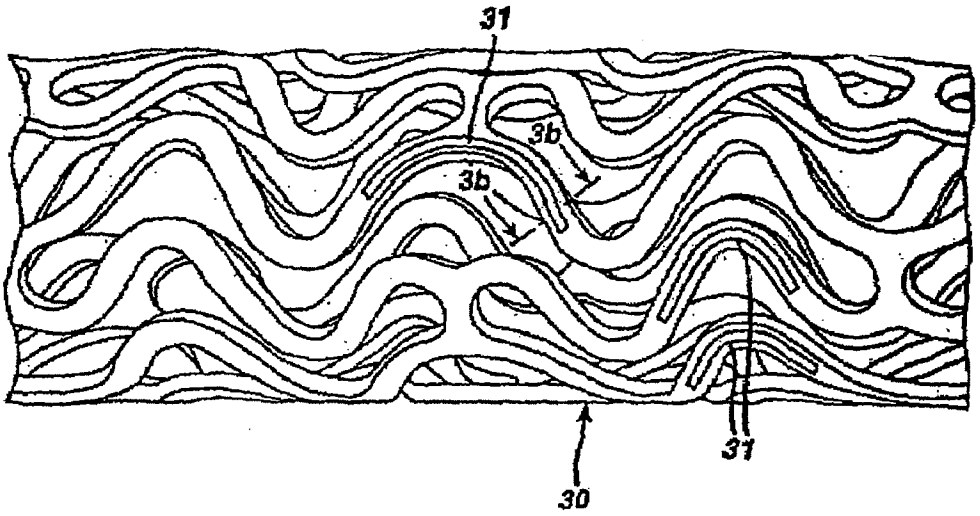


FIG. 3b

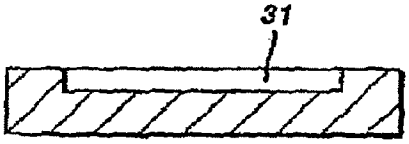
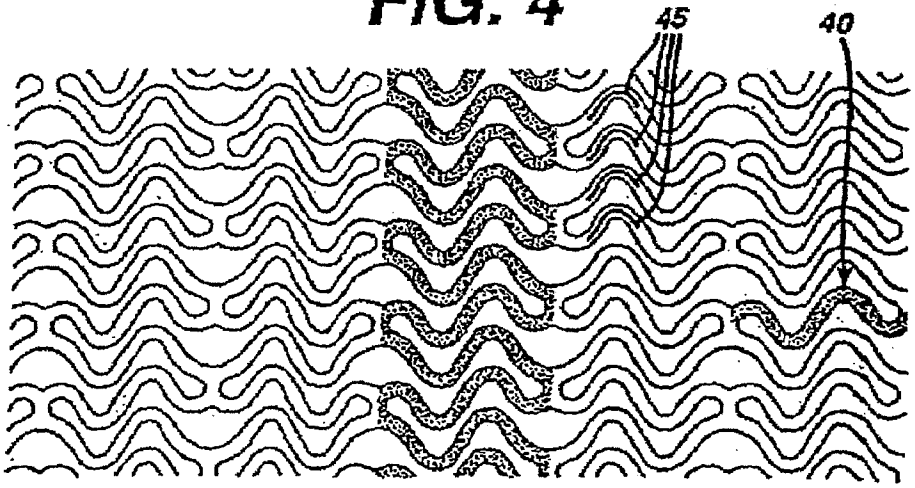


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which in turn is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosures of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a *contractile* phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF),

etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca.Ratioh, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 Circulation, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction

in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25–626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611–616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986);. Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 Neurosurgery, 92–898, (1989) colchicine (Currier, J. W. et al., 80 Circulation, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppi. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 Circulation, 1089–1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G.sub.1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.
- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.
- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.
- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.
- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.
- Extravascular delivery by the pericardial route.
- Extravascular delivery by the advential application of sustained release formulations.

Uses:

- for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.
- prevention of tumor expansion from stents.
- preventingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the

stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10.mu. to 1000.mu. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A device comprising a metallic stent, a biocompatible, nonabsorbable polymeric carrier, and a therapeutic agent, wherein:

said polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof, and

said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, and is present in an amount effective to inhibit neointimal proliferation.

2. The device according to claim **1** wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The device according to claim **1** that provides a controlled release of said therapeutic agent over a period of several weeks.

4. The device according to claim **2** that provides a controlled release of said therapeutic agent over a period of several weeks.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a device according to any one of claims **1** to **4** in the lumen of said coronary artery.

* * * * *